UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte DALE B. SCHENK

Appeal 2006-3375
Application 09/723,765
Technology Center 1600

ON BRIEF

Before SCHEINER, GRIMES, and LINCK, *Administrative Patent Judges.*

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of treating or preventing Alzheimer's disease. The Examiner has rejected the claims for obviousness-type double patenting, indefiniteness, and nonenablement. We have jurisdiction under 35 U.S.C. § 6(b). We affirm the rejections for obviousness-type double patenting but reverse the rejections for indefiniteness and nonenablement.

BACKGROUND

Alzheimer's disease is characterized by lesions in the brain known as senile plaques. (Specification 1.) "The principal constituent of the plaques is a peptide termed Aβ or β-amyloid peptide. Aβ is an internal fragment of 39-43 amino acids of a precursor protein termed amyloid precursor protein (APP)." (*Id.*)

The specification discloses "methods of preventing or treating a disease associated with amyloid deposits of Aβ in the brain of [a] patient. For example, the methods can be used to treat Alzheimer's disease. . . . Such methods entail administering fragments of Aβ or analogs thereof eliciting an immunogenic response against certain epitopes within Aβ." (Specification 4.)

DISCUSSION

1. CLAIMS

Claims 1, 14, 36, and 40-42 are pending and on appeal. Claims 1 and 36 are representative and read as follows:

1. A method of treating a patient having Alzheimer's disease, comprising administering to the patient an effective dosage to treat the disease of an N-terminal segment of Aβ (SEQ ID NO:42) consisting of residues beginning at residue 1 of Aβ and ending at residues 7-11 of Aβ and the segment being linked to a carrier molecule to form a conjugate, wherein the carrier molecule helps elicit an immune response to the N-terminal segment, and wherein if the carrier molecule is a polypeptide the polypeptide is heterologous to Aβ.

36. A method of prophylaxis of Alzheimer's disease in a patient at risk of the disease, comprising administering to the patient an effective dosage to effect prophylaxis of the disease of an N-terminal segment of Aβ (SEQ ID NO:42), the segment consisting of residues beginning at residue 1 of Aβ and ending at residues 7-11 of Aβ and the segment being linked to a carrier molecule to form a conjugate, wherein the carrier molecule helps elicit

an immune response to the N-terminal segment, and wherein if the carrier molecule is a polypeptide the polypeptide is heterologous to Aβ.

Thus, claims 1 and 36 are respectively directed to methods of treating and preventing Alzheimer's disease by administering a conjugate containing one of five fragments of Aβ: N-terminal amino acid residues 1-7, 1-8, 1-9, 1-10 or 1-11. The Aβ fragment is linked to a carrier molecule that is different from Aβ and that "helps elicit an immune response to the N-terminal segment."

2. OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1, 14, 36, and 40-42 stand rejected under the judicially created doctrine of obviousness-type double patenting as follows:

• Claims 1, 36, 41, and 42 as not patentably distinct from claims 59-104 of application 09/724,940 (now U.S. Patent 6,905,686);

• Claims 1, 14, 36, and 40-42 as not patentably distinct from claims 58, 65, 76, 78, 83, 88, 90, 99, 101, 106, 111, 113, 118, and 119 of application 09/724,567 (now U.S. Patent 6,890,535); and

• Claims 1, 14, 36, and 40-42 as not patentably distinct from claims 11, 59, 76, 88, 99, 106, and 111 of application 09/724,953 (now U.S. Patent 6,875,434).

Appellant's brief does not argue that the rejections are improper but indicates that "Appellant is prepared to file a terminal disclaimer" to overcome the rejections. (Br. 4-5.) Since Appellant has not provided any basis on which to conclude that the rejections are improper, we affirm them.

3. DEFINITENESS

Claims 1, 14, 36, and 40-42 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Examiner argues that

> the phrase 'an effective amount' is indefinite in that the claims fail to state the function to be achieved. More than one effect is implied via the specification and/or relevant art. For example the treating may require antibody production, amyloid plaque clearance, enhanced performance in cognitive function or other such symptom of a disease associated with amyloid deposi[t] of Abeta in the brain of a patient.

(Answer 19.)

Appellant argues that "the claims do indeed state the function to be achieved, that is, the dosage is effective to treat (claim 1) or effect prophylaxis (claim 36) of Alzheimer's disease." (Br. 17.) Appellant points to page 36 of the specification for definitions of treating and prophylaxis. (*Id.*)

We will reverse this rejection. As Appellant notes, the specification expressly defines the terms "therapeutically- or prophylactically-effective dose." (Specification 36, ll. 14-27). The specification defines a prophylactically effective dose as

> an amount sufficient to eliminate or reduce the risk, lessen the severity, or delay the outset of the disease, including biochemical, histologic and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of [Alzheimer's] disease.

(*Id.*, ll. 14-19.) The specification defines a therapeutically effective dose as

> an amount sufficient to cure, or at least partially arrest the symptoms of the disease (biochemical, histological and/or

> behavioral), including its complications and intermediate pathological phenotypes in development of the disease.

(*Id.*, ll. 19-23.)

Thus, when the claims are read in light of the specification, the skilled artisan would understand that the "effective dosage" recited in claims 1 and 36 means a dosage that results in at least one of the effects recited in the specification. That is, a prophylactically effective dosage would be understood to mean a dosage that reduces the likelihood of developing, lessens the severity of, or delays the onset of any of the symptoms of Alzheimer's disease, and a therapeutically effective amount would be understood to mean an amount that at least partially arrests any of the symptoms of Alzheimer's disease.

These definitions may be broad but they are not indefinite. *See In re Miller*, 441 F.2d 689, 693, 169 USPQ 597, 600 (CCPA 1971) ("[B]readth is not to be equated with indefiniteness."). We therefore reverse the rejection under 35 U.S.C. § 112, second paragraph.

4. ENABLEMENT

Claims 1, 14, 36, and 40-42 stand rejected under 35 U.S.C. § 112, first paragraph, as nonenabled. The Examiner argues that the specification does not enable the full scope of the claims, although she concedes that it is enabling for treating "PDAPP transgenic mice which over-express amyloid by administration of AN1792 (human Abeta1-42), rodent Abeta1-42, Abeta1-5 conjugated to sheep anti-mouse IgG, and Aβ1-7 in tetrameric MAP configuration as exemplified . . . [in] the specification." (Answer 7.)

PDAPP mice "exhibit Alzheimer's type overproduction and build up of beta-amyloid within the brain" and the Examiner acknowledges that the "specification teaches that the administration of particular polypeptides is able to reduce beta-amyloid within the brains" of such mice. (*Id.* at 8.) The Examiner also cites several references that "teach effective treatment of Alzheimer's disease and cognition deficits associated with amyloid plaque deposits upon beta-amyloid administration of beta-amyloid 1-28 administration." (*Id.* at 10.)

The Examiner concludes, however, that this guidance is insufficient to enable the claims. The Examiner argues that while PDAPP mice are "an art accepted animal model of Alzheimer's disease" (*id.* at 24), they do not exhibit all the characteristics of Alzheimer's disease in humans, such as paired helical filaments. (*Id.* at 13.) The Examiner also points out that the working examples in the specification include just one peptide within the scope of the present claims. (*Id.* at 14-15). The Examiner discounts the references showing removal of amyloid plaque on the basis that the "references do not teach . . . the regions or epitopes within beta-amyloid 1-42 or 1-28 peptides which are responsible for mediating plaque removal or the beneficial effects." (*Id.* at 10.)

The Examiner argues that the "specification fails to establish the structure that is required for the claimed biological activity in prophylaxis or treatment of Alzheimer's disease, and the model system is not established as predictive." (*Id.* at 14.) Thus, she concludes,

> a substantial amount of experimental trial and error [would be required] to produce a peptide of the claimed formula that also retains the biological activities recited in the claims. This trial

> and error would clearly constitute undue experimentation and, therefore, the instant specification is not enabling for the full scope of the peptides as claimed.

(*Id.*)

Appellant argues that "only five Aβ peptides (Aβ1-7, 1-8, 1-9, 1-10, and 1-11) are included in the claims." (Br. 7.) Appellant argues that making and testing these five peptides would not require a great quantity of experimentation; that the specification provides considerable guidance; that the "state of the art is advanced in that the claimed peptide conjugate can be made by standard methodology, and tested using an art-recognized transgenic mouse model"; and that the skill in the art is high. (*Id.*) Appellant concludes that when the *Wands* factors are correctly analyzed, the Examiner has not shown that the claims are nonenabled. (*Id.*)

We agree with Appellant that the Examiner has not shown that practicing the claimed method would require undue experimentation. The claims on appeal are very narrow: they require administering a conjugate that comprises one of only five fragments of Aβ. We do not agree with the Examiner's interpretation of the claims as "encompass[ing] a multitude of analogs or equivalents" (Answer 12). The claims specify "an N-terminal segment of Aβ (SEQ ID NO:42) consisting of residues beginning at residue 1 of Aβ and ending at residues 7-11 of Aβ." Thus, the claims are limited to conjugates that include an Aβ peptide consisting of the first 7, 8, 9, 10, or 11 amino acids in SEQ ID NO:42.

These peptides can be conjugated to any "carrier molecule [that] helps elicit an immune response to the N-terminal segment," other than Aβ itself, but the Examiner has not established, or even argued, that the carrier

molecule part of the conjugate would be a source of significant experimentation. Thus, for purposes of the enablement analysis, the claims are limited to methods of administering only five specific peptides.

The specification provides a working example that describes the administration of full-length Aβ (Aβ 1-42) to mice that overexpress "APP with a mutation . . . that predisposes them to develop Alzheimer's-like neuropathology." Page 47. The Examiner states that the PDAPP mouse "is an art-accepted animal model of Alzheimer's disease." (Answer 24.)

The specification states that mice treated with Aβ 1-42 had either no amyloid plaques or greatly reduced amyloid plaques in their brains, in contrast to control mice, which "contained numerous amyloid deposits." Page 49, lines 9-11. The specification concludes that "Aβ1-42 injections are highly effective in the prevention of deposition or clearance of human Aβ from brain tissue, and elimination of subsequent neuronal and inflammatory degenerative changes." Page 51, lines 2-4.

The specification describes a second experiment in which Aβ 1-42 (a.k.a. AN1792) was administered to PDAPP mice "at a time point when amyloid plaques [were] already present in the brains." Page 52, lines 22-23. The results of the experiment are said to "show that AN1792 immunization of PDAPP mice possessing existing amyloid deposits slows and prevents progressive amyloid deposition and retard[s] consequential neuropathologic changes in the aged PDAPP mouse brain." Page 60, lines 3-5.

The specification also describes an experiment in which various Aβ fragments were conjugated to a sheep antibody and their effects were compared to Aβ 1-42. Pages 60-68. The specification reports that the Aβ 1-5

conjugate brought about significant reductions in Aβ and Aβ 1-42 levels in cortex but no reduction was reported for Aβ levels in hippocampus or cerebellum; the other Aβ conjugates tested (1-12, 13-28, and 32-42, all conjugated to the same sheep antibody) were found to be ineffective in reducing Aβ levels. Page 64, line 30 to page 65, line 2.

The specification also reports the results of administering an Aβ conjugate as recited in the claims. The conjugate is described as a "multi-antigenic peptide" (MAP) in tetrameric configuration, and comprised the Aβ 1-7 peptide fused to a tetanus toxoid T-cell epitope. Page 99, line 25 to page 100, line 5. The specification reports that "the Aβ 1-7 MAP immunogen is effective in inducing a sufficient immune response significantly to retard Aβ deposition in the cortex." Page 101, lines 5-6.

Finally, the specification describes an experiment in which Aβ 1-42 was administered to monkeys and the reactivities of the resulting antibodies were mapped using fragments of Aβ. The specification reports that "in all cases the reactivity to the N-terminal peptide sequence was the predominant one." Page 104, lines 3-4. The most common additional reactivity is said to be centered around the N-terminal 10 amino acids; i.e., binding "directed to peptides covering amino acids -1–8, -1–9, and 2-11 of the AN1792 peptide. These reactivities, combined with that of the 1-10 peptide, represent the overwhelming majority of reactivity in all animals." Page 104, lines 7-9.

In our view, the working examples in the specification provide significant guidance to those of skill in the art. The working examples show *in vivo* results using an art-accepted model, they show that one peptide conjugate like that defined in the instant claims produces results similar to the

full length Aβ peptide, and they show that results produced by the full-length peptide reasonably appear to be due to an epitope in the N-terminal eleven amino acids of Aβ. We agree with Appellant that the evidence does not support the Examiner's position that undue experimentation would be required to practice the claimed methods.

As we understand it, the Examiner has two objections to the specification's working examples. First, the Examiner acknowledges that PDAPP mice are an art-accepted animal model for Alzheimer's disease, but she asserts that they are not "predictive of the results that would be expected" in humans because PDAPP mice lack some of the histological features of Alzheimer's disease, including "paired helical filaments." Examiner's Answer, page 9.

We do not agree with the Examiner that the differences between PDAPP mice and human Alzheimer's disease patients would lead those skilled in the art to doubt the predictive value of the specification's working examples. The prior art of record demonstrates that those skilled in the art accepted PDAPP mice as a useful model for testing drugs for treating Alzheimer's disease. Games[1] states that the PDAPP mouse "offers a means to test whether compounds that lower Aβ production and/or reduce its neurotoxicity *in vitro* can produce beneficial effects in an animal model prior

[1] Games et al., "Alzheimer-type neuropathology in transgenic mice overexpressing V717F β-amyloid precursor protein," *Nature*, Vol. 373, pp. 523-527 (1995).

to advancing such drugs into human trials." Page 527. Similarly, Chen[2] states that PDAPP mice "provid[e] an useful animal model for the testing of various therapeutic interventions directed toward specific aspects of the neurodegenerative process." Page 333.

The evidence shows that those skilled in the art considered PDAPP mice to be a useful animal model for testing drugs intended to treat the symptoms of Alzheimer's disease; to be useful, an animal model must provide results that are reasonably predictive of those expected in humans. Certainly, there is no guarantee that the results seen in mice will hold for humans, but enablement does not require absolute predictability. *See In re Brana*, 51 F.3d 1560,1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995): "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." (Although the *Brana* court referred to "usefulness," the rejection on appeal was for lack of enablement. *See id.* at 1568, 34 USPQ2d at 1442.)

A method of treatment can be enabled even if it has not been shown to be, and even if it never turns out to be, clinically useful. "'[O]ne who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.'" *Brana*, 51 F.3d at

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[2] Chen et al., "Neurodegenerative Alzheimer-like pathology in PDAPP 717V→F transgenic mice," *Progress in Brain Research*, Vol. 117, pp. 327-333 (1998).

1567, 34 USPQ2d at 1442 (quoting *In re Krimmel*, 292 F.2d 948, 953, 130 USPQ 215, 219 (CCPA 1961)). If those skilled in the art would reasonably expect the claimed method to produce a therapeutic effect, it can be enabled even if it has not (yet) been shown to be safe and effective in clinical trials.

The Examiner's second objection to the working examples, as we understand it, is that only one peptide within the scope of the instant claims was shown to be effective in PDAPP mice:

> There is only a single conjugate peptide amongst those claimed that is disclosed as exhibiting positive effects in the model system and that is the Aβ1-7 peptide in MAP configuration. . . . The claims are directed to a broader range of peptides. Yet no predictability is established for expecting similar function from these constructs when only a single member of the genus was effective and even[ ] then was only effective for lowering cortical Aβ levels.

Examiner's Answer, pages 14-15.

Again, we do not share the Examiner's concern. The specification shows that Aβ 1-42, Aβ 1-5 conjugated to a sheep antibody, and Aβ 1-7 conjugated to a tetanus toxoid peptide all had similar *in vivo* effects when administered to PDAPP mice. The specification also shows that the "overwhelming majority of [antigenic] reactivity in all animals" was centered around the N-terminal ten amino acids of Aβ; i.e., from amino acid -1 to amino acid 11.

In our view, the evidence of record is sufficient to lead those skilled in the art to expect that Aβ peptides 1-8, 1-9, 1-10, and 1-11 would have effects similar to Aβ 1-7 peptide when conjugated to a carrier molecule and administered to a patient.

SUMMARY

We affirm the rejections for obviousness-type double patenting. However, we reverse the rejection for indefiniteness because the specification defines what is meant by an "effective amount." We also reverse the rejection for nonenablement because the Examiner has not adequately shown that practicing the claimed methods would have required undue experimentation.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a)(1)(iv) (2006).

AFFIRMED

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